Sleep and cancer incidence in Alberta's Tomorrow Project cohort

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Abstract:

Study Objectives: Few studies have examined associations between sleep duration with combined and site-specific cancers within the same cohort. Additionally, no study to date has assessed associations between sleep timing midpoint and cancer incidence. Therefore, we aimed to investigate associations between self-reported sleep duration and sleep timing midpoint with combined and site-specific cancer incidence in Alberta's Tomorrow Project (ATP) cohort. **Methods:** The sleep duration analysis included 45,984 Albertans aged 35–69 years recruited from 2001–2015. Sleep timing midpoint (wake-time − ½ sleep duration) was assessed in a subset of ATP participants (n = 19,822). Incident cancer cases were determined through linkage with the Alberta Cancer Registry in June 2017. Cox proportional hazard regression models evaluated the effects of sleep duration and sleep timing midpoint on combined and seven site-specific cancers. **Results:** A total of 2,428 and 1,322 incident cancer cases were observed in the sleep duration and sleep timing analyses, respectively. Reporting >9 h of sleep/night versus 7–9 h of sleep/night was associated with an increased incidence of non-Hodgkin lymphoma (hazard ratio [HR] = 2.14, 95% confidence interval [CI]: 1.14–4.01; p = 0.02) and hematological (HR = 1.70, 95% CI: 1.03–2.82; p = 0.04) cancers. A later sleep timing midpoint (>4 h 8 min) versus an intermediate sleep timing midpoint (3 h 47 min–4 h 8 min) was associated with an increased incidence of combined (HR = 1.20, 95% CI: 1.04–1.37; p = 0.01) and breast (HR = 1.49, 95% CI: 1.09–2.03; p = 0.01) cancers. **Conclusions:** Sleep duration and sleep timing may play a role in cancer etiology. Studies including objective sleep assessments are needed to corroborate these findings.

Keywords: cancer incidence | cohort study | sleep duration | sleep timing

Article:

Statement of Significance
There is an increasing prevalence of regular circadian misalignment and voluntary sleep restriction in industrialized societies. This is the largest study in Canada to date to examine

associations between sleep duration with cancer incidence, and the first study to investigate associations between sleep timing midpoint with cancer incidence. Our study also assessed important effect modifiers in the sleep–cancer association (sex, body mass index, presence of medical conditions/comorbidities, alcohol intake, presence of depression, menopausal status), which suggest that other biological and behavioral components may directly impact this association. The findings from this study suggest that both sleep duration and sleep timing may impact cancer risk. Future studies including objective sleep assessments are needed to corroborate these findings.

Introduction

A Joint Consensus Statement from the American Academy of Sleep Medicine and the Sleep Research Society recommends that adults obtain at least 7 h of sleep/night for optimal health [1]. Furthermore, shorter (<7 h of sleep/night) and/or longer (>9 h of sleep/night) sleep durations have been consistently associated with a number of adverse health outcomes, such as obesity [2–6], type 2 diabetes [7–9], the metabolic syndrome [10], cardiovascular disease [11, 12], and all-cause mortality [13–16]. However, inconsistent results have been reported between sleep duration with combined and site-specific cancer risk [17–21]. More specifically, some studies reported U-shaped associations [22, 23], whereas others reported either positive [18, 24–26], inverse [27–34], or no [35–43] associations between sleep duration with combined and/or site-specific cancer incidence. Meta-analyses [17, 19–21] also did not identify any statistically significant associations between short and long sleep durations with cancer risk. These inconsistencies in results may be partly explained by the different biologic pathways hypothesized to lead to the development of cancer at different sites [18, 19]. For instance, altered metabolism leading to obesity (e.g. increased orexigenic hormones and cortisol release, altered glucoregulatory responses/insulin resistance) [44–46] and/or lower melatonin levels [28, 47, 48] that occur in response to shorter sleep durations may increase sex hormone levels and the development of hormone-related cancers [19]. Conversely, positive associations between sleep duration and cancer risk may be related to the presence of other comorbidities/chronic health conditions and/or poorer sleep quality which may increase total time in bed and confound the sleep-cancer risk association [15, 26, 49, 50].

In addition to total sleep duration, sleep timing (bed- and wake-time) has been recently associated with adverse health outcomes [51–53]. Specifically, a later sleep timing midpoint (calculated as wake-time − ½ of total sleep duration) has been associated with a higher body mass index (BMI) [51], as well as an increased risk of insulin resistance [53] and gestational diabetes [52]. Studies assessing habitual chronotypes and cancer risk have also reported that individuals with an evening or mixed (i.e. neither morning nor evening) chronotype have an increased risk of developing breast [54, 55] or prostate [40, 56, 57] cancer compared with morning chronotypes. Erren *et al.* [17] have also suggested that sleep timing and chronotype may be indirectly associated with cancer risk based on evidence that being awake during our "internal biological night" leads to disruptions in the circadian rhythm, affecting behavioral and hormonal rhythms and clock gene expressions which may accelerate tumor development. No study to date has investigated the association between sleep timing midpoint and cancer risk.

Alberta's Tomorrow Project (ATP) is a prospective cohort study that collected information on lifestyle, behavioral and environmental exposures from 2001 to 2015 in Albertans (Canada) and aims to examine the impact of these exposures on the incidence of cancer and other chronic diseases [58]. The primary aim of this article was to investigate the strength of the associations between baseline sleep duration with combined and site-specific cancer incidence among participants of ATP. Our secondary aim was to assess the strength of associations between sleep timing midpoint with combined and site-specific cancer incidence in a subset of participants from ATP.

Methods

Setting and participants

The study flow chart for these analyses is presented in Figure 1. A total of 55,530 Albertans aged 35–69 years were enrolled into a prospective cohort study between 2001 and 2015. Full details pertaining to participant recruitment, enrollment, and data collection methods for Phase I of ATP (participants enrolled between 2001 and 2008) have been described elsewhere [58]. Interested participants were mailed an information package and were considered enrolled in the study if they completed and returned the Health and Lifestyle Questionnaire and signed the consent form. Participants who were pregnant at the time of enrollment, did not consent to data linkage with the Alberta Cancer Registry (ACR) or had a personal history of cancer other than nonmelanoma skin cancer (n = 1,326) were subsequently removed from the dataset. Ethical approval was obtained from the Health Research Ethics Board of Alberta—Cancer Committee (HREBA.CC-16–0495).

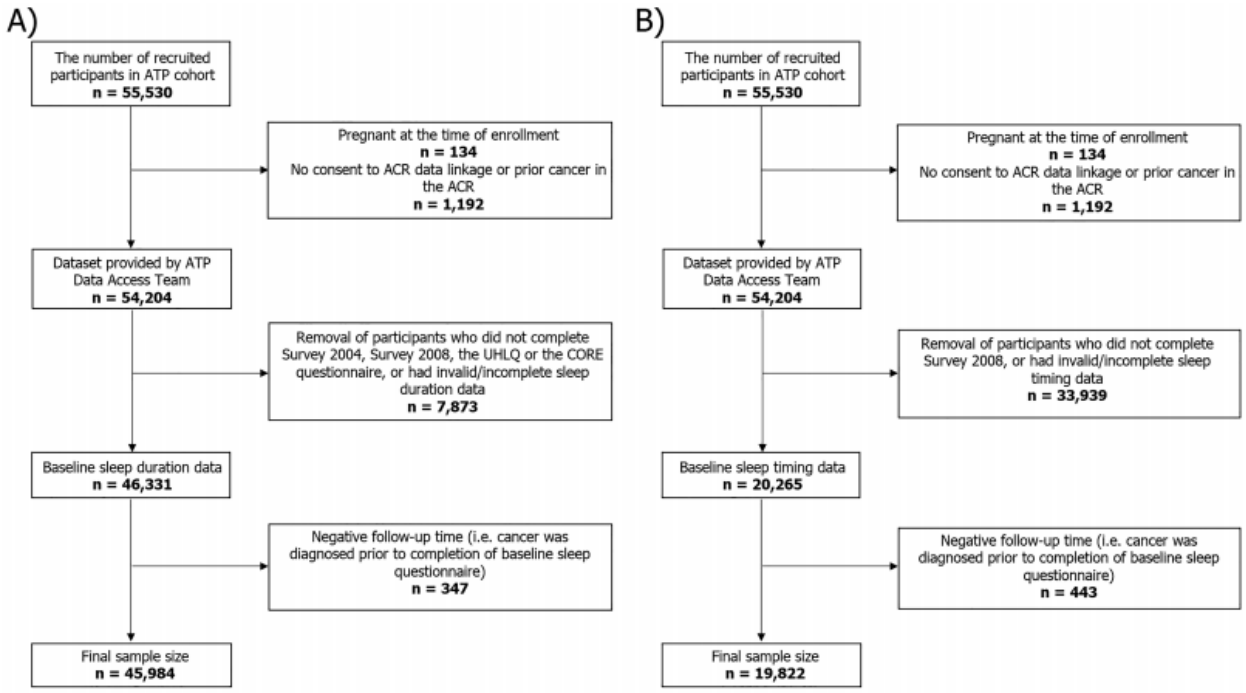


Figure 1. Study flow chart for the sleep duration (A) and sleep timing midpoint (B) analyses, Alberta's Tomorrow Project, 2001–2015.
Note: ACR, Alberta Cancer Registry; ATP, Alberta's Tomorrow Project.

Sleep assessment

Sleep duration was first self-reported by participants who completed Survey 2004 (participants enrolled from 2001 to 2003) with the following question: "On average, how many hours did you sleep each night during the past 4 weeks?" Participants who completed Survey 2008 (participants enrolled from 2001 to 2007) reported habitual bed- and wake-times with the following questions: "On average over the past 7 days, at what time did you normally go to sleep?" and "On average over the past 7 days, at what time did you normally wake up?" This information was used to derive habitual sleep duration for these participants. Sleep duration was also assessed with the Updated Health and Lifestyle Questionnaire and the CORE Questionnaire in Albertans enrolled from 2008 to 2015 as part of the Canadian Partnership for Tomorrow Project (CPTP) with the following question: "On average, how many hours per day do you usually sleep, including naps? A day refers to a 24-hour period." Baseline sleep duration (n = 46,331) was identified as the first time each participant completed one of the abovementioned questionnaires.

Bed- and wake-times were assessed in participants who completed Survey 2008 (n = 20,265). Sleep timing midpoint (wake-time − ½ of total sleep duration) was calculated for each participant since this variable has been shown to be a valid marker of sleep chronotype [59].

Cancer incidence rates

Primary cancers were identified through data linkage with the ACR using participants' personal health numbers in June 2017. The ACR is a population-based registry and it is mandatory for physicians and laboratories throughout Alberta to report all cancer cases to the ACR.

Site-specific cancers were included in the present analyses if >100 incident cases were noted in the cohort with sleep duration or sleep timing midpoint as the exposure of interest. In the sleep duration analysis, seven cancer sites were included: breast, colon (includes cancers of the colon and rectosigmoid junction), prostate, lung, endometrial, non-Hodgkin lymphoma, and hematological cancers (includes Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, multiple myeloma and plasmacytoma, and other hematopoeitic and reticuloendothelioma cancers). In the sleep timing midpoint analysis, five cancer sites were included: breast, colorectal, lung, prostate, and hematological cancers. Given that our analytical plan developed a priori was to examine sleep duration and sleep timing midpoint by categories, we selected 100 cases for inclusion in the site-specific analyses as a general threshold for reasonable statistical power to avoid reporting overly wide confidence intervals and potentially spurious associations. This approach also allowed for some degree of exploratory analyses in less common cancer sites (e.g. hematological cancers).

Covariates

Covariates in the present paper were selected based on scientific plausibility and associations between the exposure (sleep) and cancer incidence [3, 5, 7, 11, 60–65]. The cutoff points used for these covariates are based on scientific plausibility/cutoff points used in the literature and/or the distribution of responses in this cohort. These included: age (years), sex (male/female),

marital status (married or living with someone/divorced, separated, or widowed/single, never married), total household income ($0–$49,999/$50,000–$99,999/≥$100,000), highest level of education (high school or less/some posthigh school education or a posthigh school certificate or degree), employment status (yes/no), ethnicity (Caucasian/Other), smoking status (daily/occasional/former/never), alcohol intake (daily/weekly/monthly/never), BMI (<25 kg/m^2/≥25 kg/m^2), presence of at least one medical condition/comorbidity, such as cardiovascular disease, respiratory disease, diabetes (yes/no), presence of depression (yes/no), and having a family history of cancer (yes/no). For cancer sites that only included female cases (breast and endometrial cancers), menopausal status (premenopausal/postmenopausal) and gravidity (≤3 full-term pregnancies/>3 full-term pregnancies) were included in the adjusted models. Sleep duration (hours) was added as a covariate in models with sleep timing midpoint as the predictor. Data on these covariates for each participant were selected from their baseline questionnaire (i.e. the questionnaire reporting data on the sleep variable of interest) to avoid potential mediation of variables that may change over time, such as BMI, smoking status, and alcohol intake. Participants with missing data for any of these covariates were assigned a categorical value that was associated with "missing data" for each covariate (e.g. 0—BMI <25 kg/m^2, 1—BMI ≥25 kg/m^2, 2—missing value for BMI; 0—never, 1—monthly, 2—weekly, 3—daily, 4—missing value for alcohol intake). This approach was taken to avoid removal of participants with missing covariate data from the multivariate-adjusted models without modifying the association between the predictor and outcome variables within these models.

Follow-up time

The follow-up time for each participant was calculated from the date of questionnaire completion which contained their baseline sleep variable to their date of cancer diagnosis or to the end of follow-up for the present analyses. To do so, the elapsed "calendar time" (365.2425 d/year) between their exact age at questionnaire completion and their exact age at cancer diagnosis or end of follow-up was estimated. In this instance, exact age refers to the elapsed "calendar time" (365.2425 d/year) between date of birth and questionnaire completion, as well as cancer diagnosis or end of follow-up. Therefore, each participant contributed person-time from the completion of their baseline sleep questionnaire to their diagnosis of cancer or to the end of follow-up in June 2017, whichever came first.

Statistical analyses

All analyses were performed using STATA v14 (College Station, TX). Descriptive data are presented as means ± standard deviations for continuous variables and as counts and percentages for categorical variables. Differences in descriptive data between cancer cases and noncancer cases were assessed using an analysis of variance test for continuous variables and a chi-square test for categorical variables. Sleep duration was modeled as a categorical variable because of the potential U-shaped associations between sleep duration and chronic disease/all-cause mortality [6, 7, 9, 11–16]. The groupings used to define sleep duration were as follows: <7 h of sleep/night (short sleep duration), 7–9 h of sleep/night (recommended sleep duration), and >9 h of sleep/night (long sleep duration). Since no recommendations currently exist for sleep timing midpoint and the association between sleep timing midpoint and cancer incidence is unknown, we created tertiles to compare an intermediate sleep timing midpoint (referent group) within this

sample to an earlier and later sleep timing midpoint. Cutoff points to define earlier and later sleep timing midpoints have been used in previous studies [51, 52]. The cutoff points used to define tertiles in our sample are comparable to those used in the aforementioned studies [51, 52] and a population-based sample that identified 4 h 00 min as the 50th percentile for sleep timing midpoint [66].

Cox proportional hazards regression models were conducted to estimate multivariate-adjusted hazards ratios (HR) and 95% confidence intervals (95% CIs) between sleep duration (7–9 h of sleep/night as the referent group) or sleep timing midpoint (intermediate sleep timing midpoint as the referent group) groups with combined and site-specific cancer incidence. We formally tested the proportional hazards assumption for the combined and site-specific cancer incidence models and found no evidence of statistically significant differences ($p < 0.05$) in hazard across the follow-up period between sleep duration and sleep timing midpoint categories (results not shown). To address the potential issue of reverse causality (i.e. sleep could be influenced by physiological changes incurred as a result of an existing but undiagnosed cancer), we repeated the risk analyses after excluding cancer cases that were diagnosed <2 years (730.5 days) after baseline sleep data collection.

Lastly, we examined potential effect modification for the association between sleep duration and sleep timing midpoint with combined cancer incidence in the multivariate-adjusted models by the following covariates: sex (male/female), BMI (<25 kg/m^2/≥25 kg/m^2), presence of medical conditions/comorbidities (yes/no), and presence of depression (yes/no). Effect modification for the association between sleep duration with alcohol intake (daily/weekly/monthly/never) and menopausal status (premenopausal/postmenopausal) were also tested. Statistical significance was set at $p < 0.05$.

Results

Participant characteristics, according to sex and case status, for 45,984 participants (16,557 males and 29,427 females) included in the sleep duration analysis are presented in Table 1. Of these, a total of 2,428 participants (1,038 males and 1,390 females) were diagnosed with cancer during the study follow-up period. The mean follow-up times for cancer and noncancer cases were 4.78 ± 3.20 and 7.47 ± 3.25 years, respectively, yielding a total of 336,892 person-years of follow-up. Cancer cases were older, had longer sleep durations and a higher BMI compared to noncancer cases. A larger proportion of cancer cases were also Caucasian, less educated, had a lower total household income, were unemployed, were daily smokers, had at least one medical condition/comorbidity, had a family history of cancer and were postmenopausal (females only) compared with noncancer cases.

Table 1. Descriptive statistics for Alberta's Tomorrow Project study participants who provided data on sleep duration and consented to data linkage, *n* = 45,984, 2001–2015

	Mean (standard deviation and/or standard error of the mean*) or *N* (%)						
	Male cancer cases (*n* = 1038)	**Male noncancer cases (*n* = 15,519)**	**Female cancer cases (*n* = 1,390)**	**Females noncancer cases (*n* = 28,037)**	**All cancer cases (*n* = 2,428)**	**All noncancer cases (*n* = 43,556)**	***P*-value†**
Follow-up time (years)	4.81 (3.26)	7.68 (3.28)	4.76 (3.16)	7.35 (3.22)	4.78 (3.20)	7.47 (3.25)	**<0.0001**
Sleep duration (h:min)	7 h 29 min (1 h 13 min)	7 h 22 min (1 h 5 min)	7 h 33 min (1 h 20 min)	7 h 31 min (1 h 11 min)	7 h 31 min (1 h 17 min)	7 h 27 min (1 h 9 min)	**0.01**
Sleep duration category							
Recommended sleep duration	754 (72.6%)	11,120 (71.7%)	972 (69.9%)	20,665 (73.7%)	1,726 (71.1%)	31,785 (73.0%)	0.61
Short sleep duration	229 (22.1%)	3,782 (24.4%)	302 (21.7%)	5,721 (20.4%)	531 (21.9%)	9,503 (21.8%)	1.00
Long sleep duration	55 (5.3%)	617 (4.0%)	116 (8.4%)	1,651 (5.9%)	171 (7.0%)	2,268 (5.2%)	**0.001**
Age (years)*	60.0 (7.7, 0.24)	53.8 (9.3, 0.07)	58.0 (8.8, 0.24)	52.8 (9.2, 0.05)	58.9 (8.4, 0.17)	53.2 (9.3, 0.04)	**<0.0001**
Body mass index (kg/m^2)*	28.7 (4.6, 0.15)	27.9 (4.4, 0.04)	28.2 (6.3, 0.19)	27.0 (5.8, 0.04)	28.4 (5.6, 0.12)	27.4 (5.3, 0.03)	**<0.0001**
Body mass index category							
Body mass index <25 kg/m^2	165 (15.9%)	3,030 (19.5%)	397 (28.6%)	8,994 (32.1%)	562 (23.2%)	12,024 (27.6%)	**0.0002**
Body mass index ≥25 kg/m^2	745 (71.8%)	9,266 (59.7%)	757 (54.5%)	11,920 (42.5%)	1,502 (61.9%)	21,186 (48.6%)	**<0.0001**
Missing	128 (12.3%)	3,223 (20.8%)	236 (17.0%)	7,123 (25.4%)	364 (15.0%)	10,346 (23.8%)	**<0.0001**
Ethnicity							
Caucasian	911 (87.8%)	12,568 (81.0%)	1,176 (84.6%)	22,562 (80.5%)	2,087 (86.0%)	35,130 (80.7%)	**0.02**
Other	61 (5.9%)	1,509 (9.7%)	96 (6.9%)	2,420 (8.6%)	157 (6.5%)	3,929 (9.0%)	**0.0002**
Missing	66 (6.4%)	1,442 (9.3%)	118 (8.5%)	3,055 (10.9%)	184 (7.6%)	4,497 (10.3%)	**0.0002**
Marital status							
Married or living with someone	865 (83.3%)	12,975 (83.6%)	991 (71.3%)	21,085 (75.2%)	1,856 (76.4%)	34,060 (78.2%)	0.64
Divorced, separated or widowed	125 (12.0%)	1,530 (9.9%)	317 (22.8%)	5,119 (18.3%)	442 (18.2%)	6,649 (15.3%)	**0.002**
Single, never married	48 (4.6%)	1,009 (6.5%)	82 (5.9%)	1,824 (6.5%)	130 (5.4%)	2,833 (6.5%)	0.10
Missing	0 (0%)	5 (0.1%)	0 (0%)	9 (0.1%)	0 (0%)	14 (0.03%)	0.67
Education							
High school or less	264 (25.4%)	2,834 (18.3%)	382 (27.5%)	6,103 (21.8%)	646 (26.6%)	8,937 (20.5%)	**<0.0001**
Some post-high school education or a post-high school degree or certificate	691 (66.6%)	12,093 (77.9%)	890 (64.0%)	21,104 (75.3%)	1,581 (65.1%)	33,197 (76.2%)	**<0.0001**
Missing	83 (8.0%)	592 (3.8%)	118 (8.5%)	830 (3.0%)	201 (8.3%)	1,422 (3.3%)	**<0.0001**
Total household income							
$0–$49,999	208 (20.0%)	1,923 (12.4%)	372 (26.8%)	5,260 (18.8%)	580 (23.9%)	7,183 (16.5%)	**<0.0001**
$50,000–$99,999	360 (34.7%)	4,655 (30.0%)	450 (32.4%)	8,437 (30.1%)	810 (33.4%)	13,092 (30.1%)	**0.02**
≥$100,000	341 (32.9%)	7,734 (49.8%)	362 (26.0%)	11,721 (41.8%)	703 (29.0%)	19,455 (44.7%)	**<0.0001**
Missing	129 (12.4%)	1,207 (7.8%)	206 (14.8%)	2,619 (9.3%)	335 (13.8%)	3,826 (8.8%)	**<0.0001**

	Mean (standard deviation and/or standard error of the mean*) or *N* (%)						
	Male cancer cases	**Male noncancer cases**	**Female cancer cases**	**Females noncancer cases**	**All cancer cases**	**All noncancer cases**	***P*-value[†]**
	(*n* = 1038)	**(*n* = 15,519)**	**(*n* = 1,390)**	**(*n* = 28,037)**	**(*n* = 2,428)**	**(*n* = 43,556)**	
Employment status							
Yes	652 (62.8%)	12,085 (77.9%)	728 (52.4%)	18,660 (66.6%)	1,380 (56.8%)	30,745 (70.6%)	**<0.0001**
No	386 (37.2%)	3,417 (22.0%)	662 (47.6%)	9,355 (33.4%)	1,048 (43.2%)	12,772 (29.3%)	**<0.0001**
Missing	0 (0%)	17 (0.1%)	0 (0%)	22 (0.1%)	0 (0%)	39 (0.1%)	0.33
Alcohol intake							
Never	132 (12.7%)	1,609 (10.4%)	201 (14.5%)	3,123 (11.1%)	333 (13.7%)	4,732 (10.9%)	**0.0002**
Monthly	243 (23.4%)	4,093 (26.4%)	537 (38.6%)	11,205 (40.0%)	780 (32.1%)	15,298 (35.1%)	0.05
Weekly	423 (40.8%)	6,695 (43.1%)	360 (25.9%)	9,541 (34.0%)	783 (32.3%)	16,236 (37.3%)	**0.0004**
Daily	121 (11.7)	1,521 (9.8%)	96 (6.9%)	1,618 (5.8%)	217 (8.9%)	3,139 (7.2%)	**0.01**
Missing	119 (11.5%)	1,601 (10.3%)	196 (14.1%)	2,550 (9.1%)	315 (13.0%)	4,151 (9.5%)	**<0.0001**
Smoking status							
Never	563 (54.2%)	8,875 (57.2%)	760 (54.7%)	16,631 (59.3%)	1,323 (54.5%)	25,506 (58.6%)	**0.04**
Former	318 (30.6%)	4,842 (31.2%)	385 (27.7%)	8,631 (30.8%)	703 (29.0%)	13,473 (30.9%)	0.23
Occasional	26 (2.5%)	438 (2.8%)	25 (1.8%)	560 (2.0%)	51 (2.1%)	998 (2.3%)	0.82
Daily	131 (12.6%)	1,333 (8.6%)	220 (15.8%)	2,175 (7.8%)	351 (14.5%)	3,508 (8.1%)	**<0.0001**
Missing	0 (0%)	31 (0.2%)	0 (0%)	40 (0.1%)	0 (0%)	71 (0.2%)	0.14
Presence of at least one medical condition or comorbidity							
No	293 (28.2%)	6,315 (40.7%)	327 (23.5)	9,476 (33.8%)	620 (25.5%)	15,791 (36.3%)	**<0.0001**
Yes	741 (71.4%)	9,127 (58.8%)	1,060 (76.3%)	18,487 (65.9%)	1,801 (74.2%)	27,614 (63.4%)	**<0.0001**
Missing	4 (0.4%)	77 (0.5%)	3 (0.2%)	74 (0.3%)	7 (0.3%)	151 (0.4%)	0.90
Presence of depression							
No	470 (45.3%)	9,081 (58.5%)	595 (42.8%)	15,747 (56.2%)	1,065 (43.9%)	24,828 (57.0%)	**<0.0001**
Yes	138 (13.3%)	1,924 (12.4%)	291 (20.9%)	5,234 (18.7%)	429 (17.7%)	7,158 (16.4%)	0.35
Missing	430 (41.4%)	4,514 (29.1%)	504 (36.3%)	7,056 (25.2%)	934 (38.5%)	11,570 (26.6%)	**<0.0001**
Menopausal status							
Premenopausal	NA	NA	304 (21.9%)	10,990 (39.2%)			**<0.0001**
Postmenopausal	NA	NA	879 (63.2%)	14,317 (51.1%)			**<0.0001**
Missing	NA	NA	207 (14.9%)	2,730 (9.7%)			**<0.0001**
Gravidity	NA	NA	2.5 (1.2, 0.03)	2.3 (1.2, 0.01)			**<0.0001**
Gravidity category							
≤3 full-term pregnancies	NA	NA	1,015 (73.0%)	21,476 (76.6%)			0.33
>3 full-term pregnancies	NA	NA	219 (15.8%)	2,777 (9.9%)			**<0.0001**
Missing	NA	NA	156 (11.2%)	3,784 (13.5%)			0.08
Family history of cancer							

	Mean (standard deviation and/or standard error of the mean*) or *N* (%)						
	Male cancer cases	**Male noncancer cases**	**Female cancer cases**	**Females noncancer cases**	**All cancer cases**	**All noncancer cases**	***P*-value†**
	(*n* = 1038)	**(*n* = 15,519)**	**(*n* = 1,390)**	**(*n* = 28,037)**	**(*n* = 2,428)**	**(*n* = 43,556)**	
No	589 (56.7%)	11,433 (73.7%)	789 (56.8%)	20,753 (74.0%)	1,378 (56.8%)	32,186 (73.9%)	**<0.0001**
Yes	449 (43.3%)	4,086 (26.3%)	601 (43.2%)	7,284 (26.0%)	1,050 (43.3%)	11,370 (26.1%)	**<0.0001**

NA, not applicable.

*The standard deviation and standard error of the mean are presented for continuous age and body mass index variables.

†*p*-Values for the differences in descriptive data between all cancer cases and all noncancer cases. Bold values indicate statistically significant differences in descriptive data between cancer and noncancer cases, which is set at $p < 0.05$.

Table 2. Descriptive statistics for Alberta's Tomorrow Project study participants who have data on sleep timing midpoint and consented to data linkage, *n* = 19,822, 2001–2015

	Mean (standard deviation and/or standard error of the mean*) or *N* (%)						
	Male cancer cases	**Male noncancer cases**	**Female cancer cases**	**Females noncancer cases**	**All cancer cases**	**All noncancer cases**	***P*-value†**
	(n = 585)	**(*n* = 6,933)**	**(*n* = 737)**	**(*n* = 11,567)**	**(*n* = 1,322)**	**(*n* = 18,500)**	
Follow-up time (years)	4.56 (2.49)	8.71 (0.23)	4.41 (2.45)	8.70 (0.22)	4.48 (2.46)	8.70 (0.22)	**<0.0001**
Sleep timing midpoint (clock time)	3:59 am (33 min)	3:53 am (32 min)	4:04 am (34 min)	4:02 am (32 min)	4:02 am (34 min)	3:58 am (32 min)	0.05
Sleep timing midpoint category							
Intermediate sleep timing midpoint	198 (33.9%)	2,389 (34.5%)	207 (28.1%)	4,044 (35.0%)	405 (30.6%)	6,433 (34.8%)	0.05
Early sleep timing midpoint	193 (33.0%)	2,811 (40.6%)	207 (28.1%)	3,136 (27.1%)	400 (30.3%)	5,947 (32.2%)	0.50
Late sleep timing midpoint	194 (33.2%)	1,733 (25.0%)	323 (43.8%)	4,387 (37.9%)	517 (39.1%)	6,120 (33.1%)	**0.001**
Sleep duration (h:min)	7 h 46 min (1 h 12 min)	7 h 35 min (1 h 5 min)	7 h 50 min (1 h 18 min)	7 h 52 min (1 h 8 min)	7 h 48 min (1 h 16 min)	7 h 46 min (1 h 8 min)	0.20
Age (years)*	61.1 (8.1, 0.33)	55.0 (8.9, 0.11)	60.3 (8.8, 0.32)	55.0 (9.1, 0.08)	60.7 (8.5, 0.23)	55.0 (9.0, 0.07)	**<0.0001**
Body mass index (kg/m^2)*	28.8 (4.8, 0.20)	28.1 (4.4, 0.05)	28.2 (6.1, 0.23)	27.3 (5.8, 0.05)	28.5 (5.6, 0.16)	27.6 (5.4, 0.04)	**<0.0001**
Body mass index category							
Body mass index <25 kg/m^2	112 (19.2%)	1,543 (22.3%)	235 (31.9%)	4,593 (39.7%)	347 (26.3%)	6,136 (33.2%)	**0.0001**
Body mass index ≥25kg/m^2	467 (79.8%)	5,320 (76.7%)	487 (66.1%)	6,760 (58.4%)	954 (72.2%)	12,080 (65.3%)	**0.01**
Missing	6 (1.0%)	70 (1.0%)	15 (2.0%)	214 (1.9%)	21 (1.6%)	284 (1.5%)	1.00
Ethnicity							
Caucasian	550 (94.0%)	6,333 (91.4%)	689 (93.5%)	10,638 (92.0%)	1,239 (93.7%)	16,971 (91.7%)	0.78
Other	34 (5.8%)	565 (8.2%)	44 (6.0%)	877 (7.6%)	78 (5.9%)	1,442 (7.8%)	0.06
Missing	1 (0.2%)	35 (0.5%)	4 (0.5%)	52 (0.5%)	5 (0.4%)	87 (0.5%)	0.90
Marital status							
Married or living with someone	493 (84.3%)	5,825 (84.0%)	528 (71.6%)	8,793 (76.0%)	1,021 (77.2%)	14,618 (79.0%)	0.78
Divorced, separated or widowed	64 (10.9%)	695 (10.0%)	173 (23.5%)	2,220 (19.2%)	237 (17.9%)	2,915 (15.8%)	0.16
Single, never married	28 (4.8%)	405 (5.8%)	36 (4.9%)	540 (4.7%)	64 (4.8%)	945 (5.1%)	0.90
Missing	0 (0%)	8 (0.1%)	0 (0%)	14 (0.1%)	0 (0%)	22 (0.1%)	0.45
Education							

	Mean (standard deviation and/or standard error of the mean*) or *N* (%)						
	Male cancer cases (n = 585)	**Male noncancer cases (*n* = 6,933)**	**Female cancer cases (*n* = 737)**	**Females noncancer cases (*n* = 11,567)**	**All cancer cases (*n* = 1,322)**	**All noncancer cases (*n* = 18,500)**	***P*-value†**
High school or less	183 (31.3%)	1,593 (23.0%)	244 (33.1%)	3,136 (27.1%)	427 (32.3%)	4,729 (25.6%)	**<0.0001**
Some post-high school education or a post-high school degree or certificate	401 (68.6%)	5,330 (76.9%)	493 (66.9%)	8,420 (72.8%)	894 (67.6%)	13,750 (74.3%)	**0.02**
Missing	1 (0.2%)	10 (0.1%)	0 (0%)	11 (0.1%)	1 (0.1%)	21 (0.1%)	0.90
Total household income							
$0–$49,999	130 (22.2%)	1,051 (15.2%)	224 (30.4%)	2,814 (24.3%)	354 (26.8%)	3,865 (20.9%)	**<0.0001**
$50,000–$99,999	219 (37.4%)	2,273 (32.8%)	261 (35.4%)	3,565 (30.8%)	480 (36.3%)	5,838 (31.6%)	**0.01**
≥$100,000	192 (32.8%)	3,226 (46.5%)	163 (22.1%)	4,046 (35.0%)	355 (26.9%)	7,272 (39.3%)	**<0.0001**
Missing	44 (7.5%)	386 (5.5%)	89 (12.1%)	1,142 (9.9%)	133 (10.1%)	4,387 (37.9%)	0.09
Employment status							
Yes	354 (60.5%)	5,362 (77.3%)	352 (47.8%)	7,179 (62.1%)	706 (53.4%)	12,541 (67.8%)	**<0.0001**
No	231 (39.5%)	1,562 (22.5%)	385 (52.2%)	4,374 (37.8%)	616 (46.6%)	5,936 (32.1%)	**<0.0001**
Missing	0 (0%)	9 (0.1%)	0 (0%)	14 (0.1%)	0 (0%)	23 (0.1%)	0.45
Smoking status							
Never	220 (37.6%)	3,277 (47.3%)	315 (42.7%)	6,009 (52.0%)	535 (40.5%)	9,286 (50.2%)	**<0.0001**
Former	274 (46.8%)	2,675 (38.6%)	285 (38.7%)	4,115 (35.6%)	559 (42.3%)	6,790 (36.7%)	**0.01**
Occasional	8 (1.4%)	182 (2.6%)	17 (2.3%)	222 (1.9%)	25 (1.9%)	404 (2.2%)	0.78
Daily	80 (13.7%)	790 (11.4%)	118 (16.0%)	1,196 (10.3%)	198 (15.0%)	1,986 (10.7%)	**<0.0001**
Missing	3 (0.5%)	9 (0.1%)	2 (0.3%)	25 (0.2%)	5 (0.4%)	34 (0.2%)	0.30
Presence of at least one medical condition or comorbidity							
No	99 (16.9%)	2,031 (29.3%)	132 (17.9)	2,990 (25.9%)	231 (17.5%)	5,021 (27.1%)	**<0.0001**
Yes	483 (82.6%)	4,890 (70.5%)	603 (81.8%)	8,565 (74.1%)	1,086 (82.2%)	13,455 (72.7%)	**0.001**
Missing	3 (0.5%)	12 (0.2%)	2 (0.3%)	12 (0.1%)	5 (0.4%)	24 (0.1%)	0.07
Presence of depression							
No	456 (78.0%)	5,311 (76.6%)	536 (72.7%)	8,234 (71.2%)	992 (75.0%)	13,545 (73.2%)	0.74
Yes	129 (22.1%)	1,610 (23.2%)	199 (27.0%)	3,311 (28.6%)	328 (24.8%)	4,921 (26.6%)	0.47
Missing	0 (0%)	12 (0.2%)	2 (0.2%)	22 (0.2%)	2 (0.2%)	34 (0.2%)	0.95
Gravidity	NA	NA	2.6 (1.2, 0.05)	2.5 (1.2, 0.01)			**0.002**
Gravidity category							
≤3 full-term pregnancies	NA	NA	536 (72.7%)	8,799 (76.1%)			**<0.0001**
>3 full-term pregnancies	NA	NA	130 (17.6%)	1,541 (13.3%)			**<0.0001**
Missing	NA	NA	71 (9.6%)	1,227 (10.6%)			0.64
Family history of cancer							
No	248 (42.4%)	3,417 (49.3%)	282 (38.3%)	5,194 (44.9%)	530 (40.1%)	8,611 (46.6%)	**0.004**
Yes	337 (57.6%)	3,516 (50.7%)	455 (61.7%)	6,373 (55.1%)	792 (59.9%)	9,889 (53.5%)	**0.01**

NA, not applicable.

*The standard deviation and standard error of the mean are presented for continuous age and body mass index variables.

†*p*-Values for the differences in descriptive data between all cancer cases and all noncancer cases.

A U-shaped association between sleep duration, modeled as a continuous variable and adjusted for covariates, and combined cancer risk was observed (Figure 2). However, when presented as a categorical variable, short and long sleep durations were not significantly associated with combined cancer risk in the multivariate- and latency multivariate-adjusted models (Figure 3). For site-specific cancer incidence, long sleep duration was associated with an increased risk of non-Hodgkin lymphoma and hematological cancers in the multivariate- and latency multivariate-adjusted models (Figure 3).

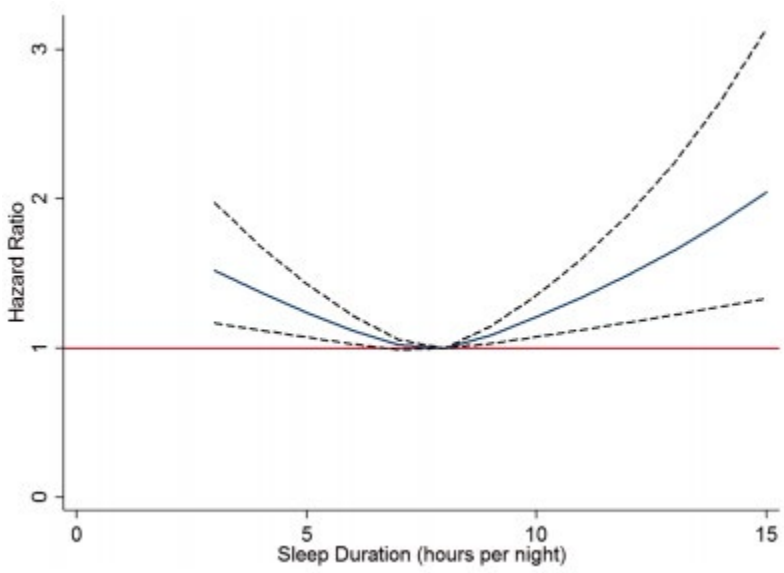


Figure 2. Effects of sleep duration modeled as a continuous variable on combined cancer risk for 45,984 participants in Alberta's Tomorrow Project.
Note: The model was adjusted for age, sex, total household income, employment status, marital status, education, ethnicity, alcohol intake, smoking status, body mass index, presence of at least one medical conditions/comorbidity, presence of depression, family history of cancer.

The sleep duration × medical condition ($p = 0.002$) and sleep duration × menopausal status ($p = 0.001$) interaction terms were associated with combined cancer incidence when added to the multivariate-adjusted model. However, sleep duration × sex ($p = 0.30$), sleep duration × BMI ($p = 0.23$), sleep duration × depression ($p = 0.68$) and sleep duration × alcohol intake ($P = 0.17$) interaction terms were not associated with combined cancer incidence in the multivariate-adjusted model. When testing for effect modification, short sleep duration was associated with an increased risk of combined cancer incidence in females, but not males, as well as postmenopausal but not premenopausal females (Figure 4). Similarly, short sleep duration was associated with an increased risk of combined cancer incidence in daily alcohol drinkers, which was not present in participants who reported weekly, monthly, or no alcohol intake, as well as participants who reported having depression versus those who reported no depression (Figure 4). Lastly, both short and long sleep durations were associated with an increased risk of combined cancer incidence in participants who reported at least one medical condition/comorbidity, but not in participants who reported an absence of medical conditions/comorbidities (Figure 4).

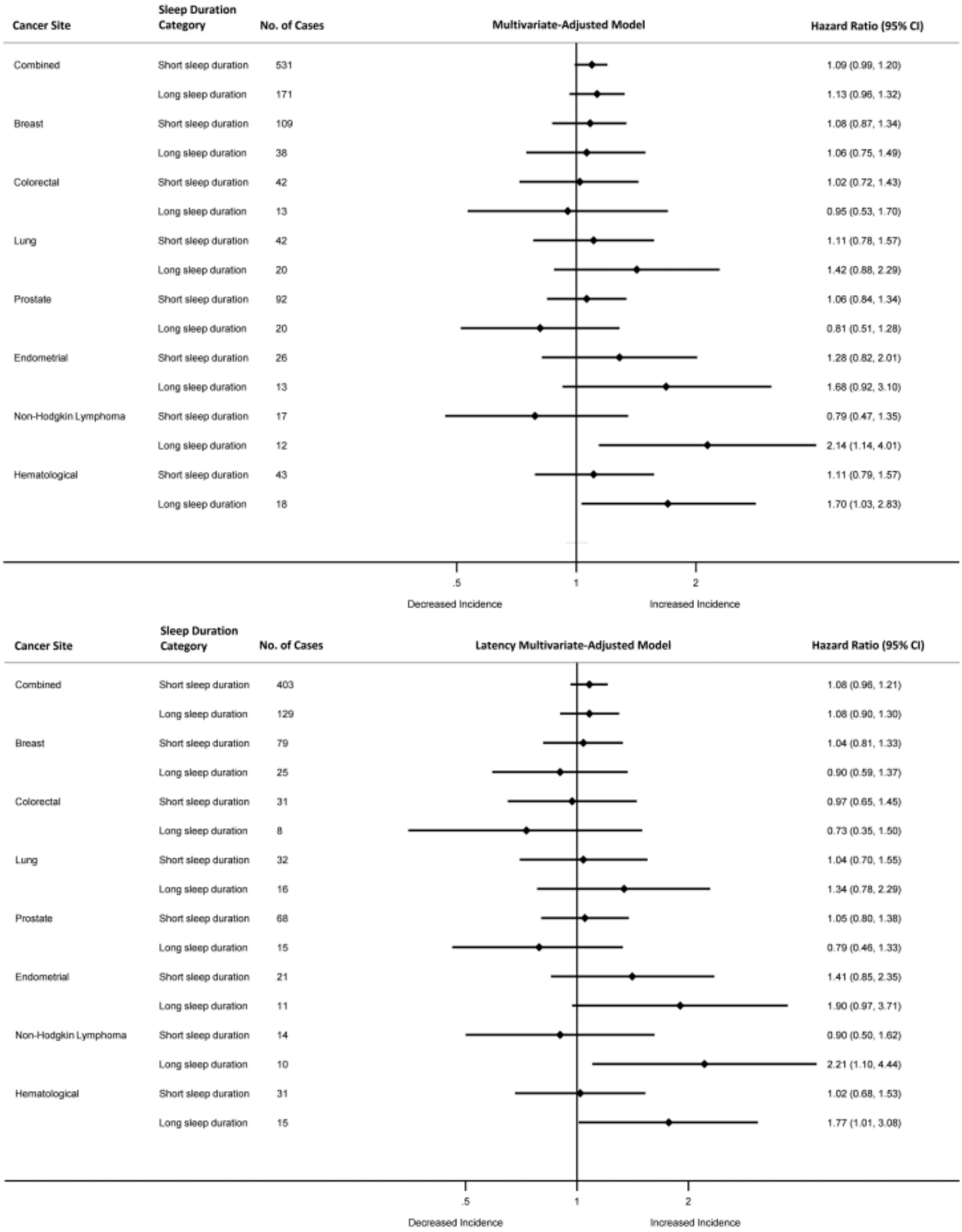


Figure 3. Cox regression hazard ratios of combined and site-specific cancer incidence and sleep duration groups for 45,984 participants in Alberta's Tomorrow Project.

Note: Recommended sleep duration (Ref) = 7–9 h/night, short sleep duration < 7 h/night, long sleep duration > 9 h/night. The multivariate-adjusted models included the following covariates: age, sex (nonsex-specific cancers),

total household income, employment status, marital status, education, ethnicity, alcohol intake, smoking status, body mass index, presence of at least one medical conditions/comorbidity, presence of depression, family history of cancer, menopausal status, and gravidity (breast and endometrial cancers only). The latency multivariate-adjusted models removed cancer cases diagnosed <2 years after questionnaire completion. $^{**}p < 0.01$, $^{*}p < 0.05$. HR, hazard ratio; CI, confidence interval.

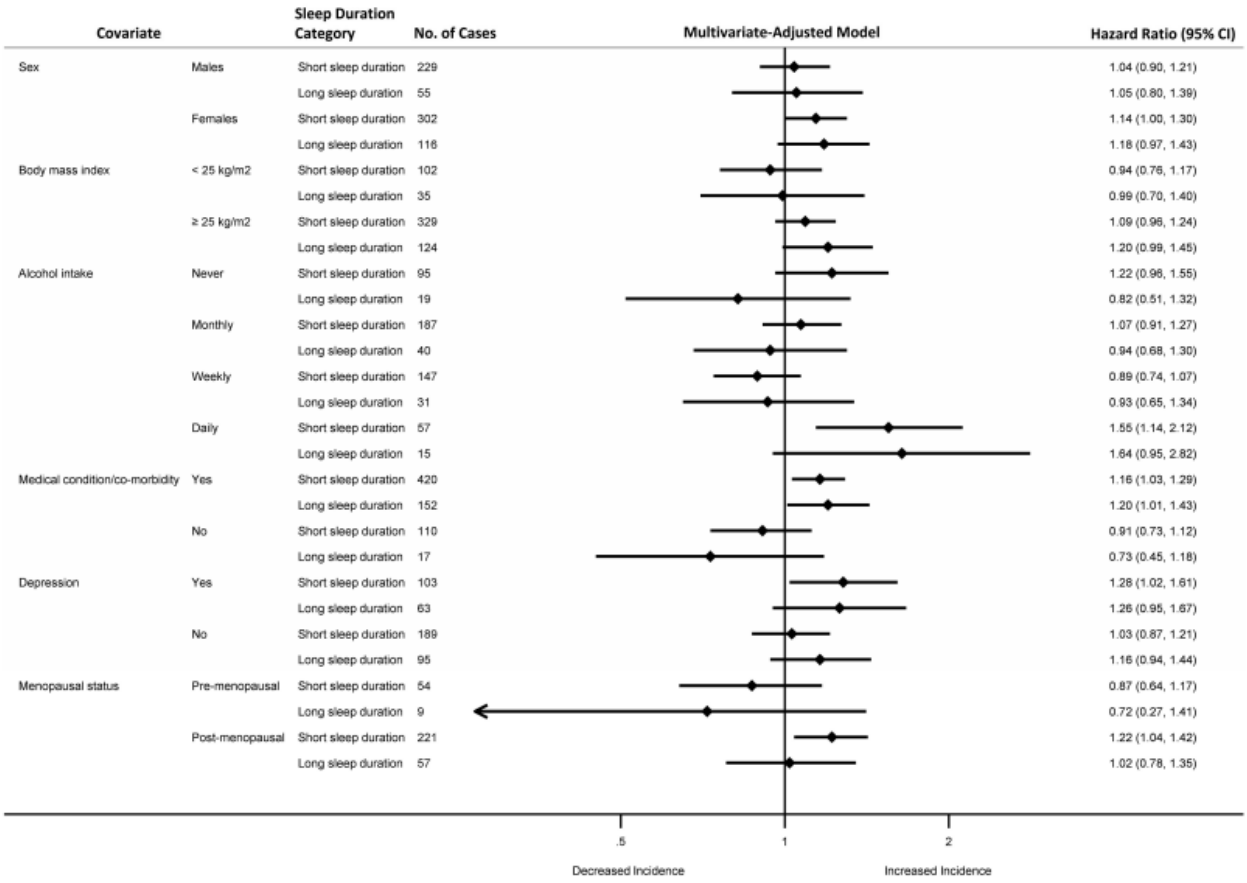
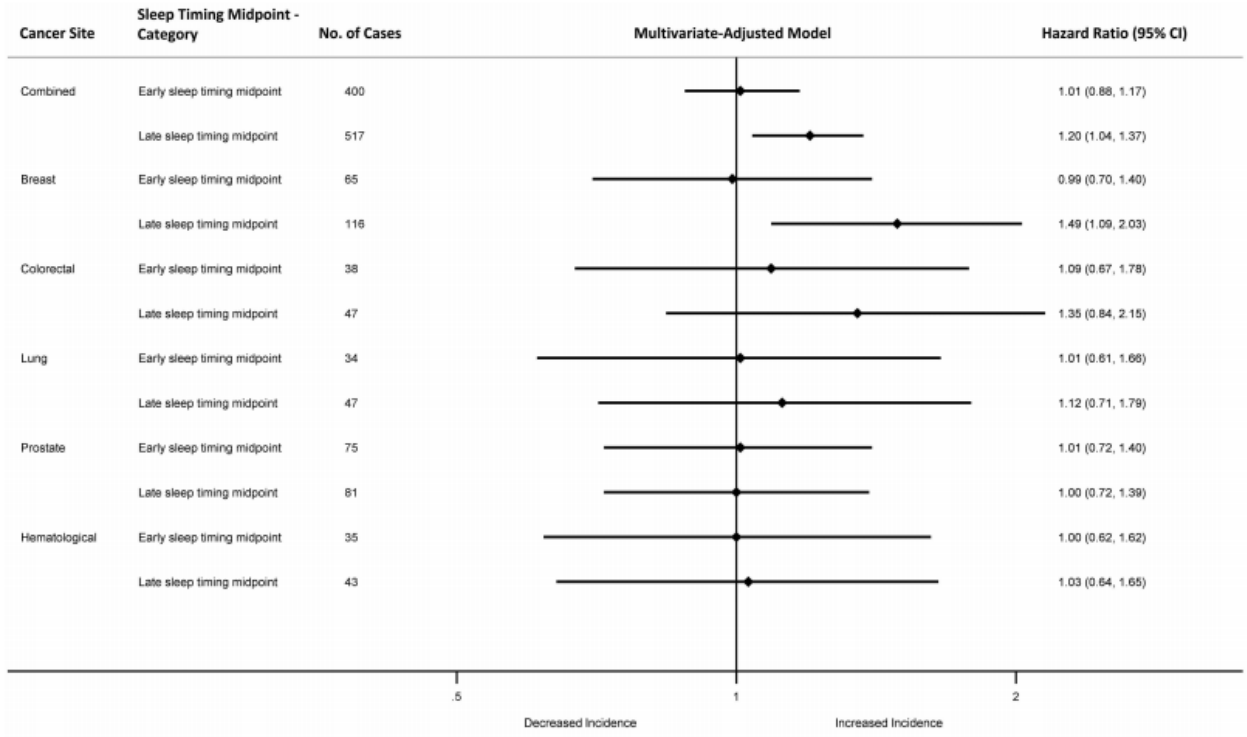


Figure 4. Cox regression hazard ratios of combined cancer incidence and sleep duration groups, stratified by sex, body mass index, alcohol intake, presence of at least one medical condition/comorbidity, presence of depression or menopausal status (females only) for 45,984 participants in Alberta's Tomorrow Project.

Note: Recommended sleep duration (Ref) = 7–9 h/night, short sleep duration < 7 h/night, long sleep duration > 9 h/night. The model was adjusted for age, sex (if not stratified variable and menopausal status as effect modifier), total household income, employment status, marital status, education, ethnicity, alcohol intake (if not stratified variable), smoking status, body mass index (if not stratified variable), presence of at least one medical conditions/comorbidity (if not stratified variable), presence of depression (if not stratified variable), family history of cancer. $^{**}p < 0.01$, $^{*}p < 0.05$. HR, hazard ratio; CI, confidence interval.



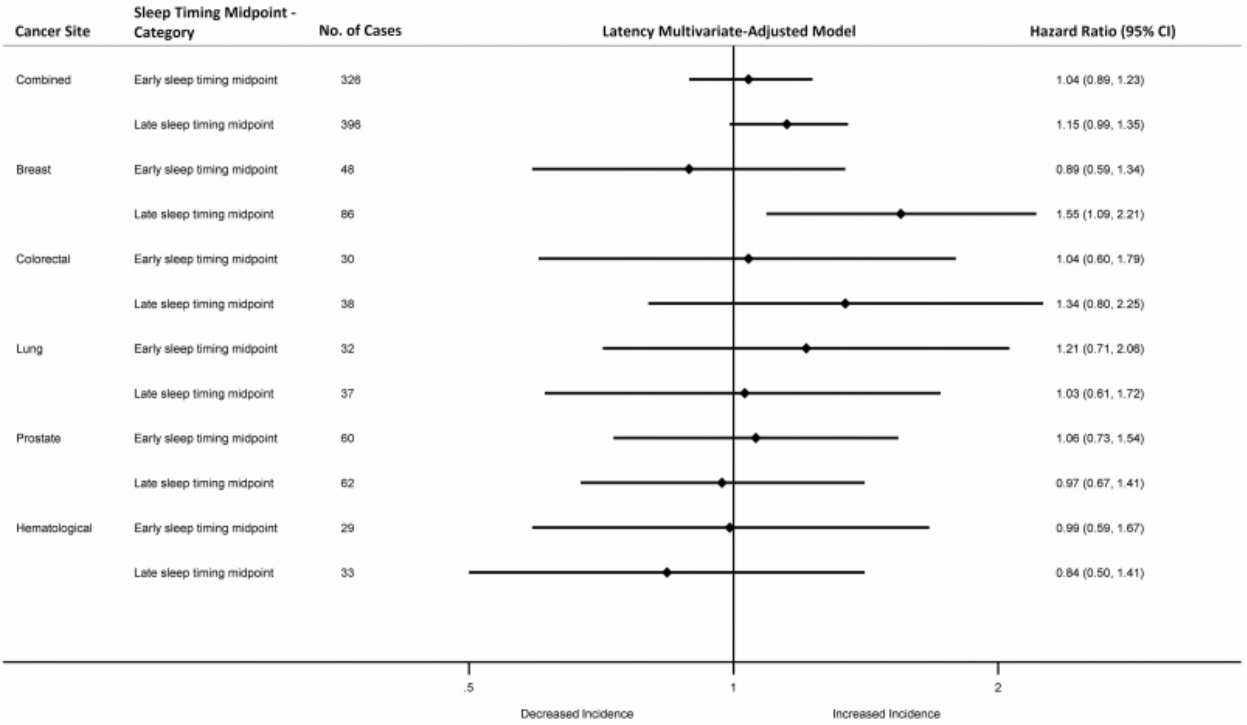


Figure 5. Cox regression hazard ratios of combined and site-specific cancer incidence and sleep timing midpoint tertiles for 19,822 participants in Alberta's Tomorrow Project.

Note: Intermediate sleep timing midpoint (Ref) = 3 h 47 min–4 h 8 min, early sleep timing midpoint < 3 h 47 min, late sleep timing midpoint > 4 h 8 min. The multivariate-adjusted models included the following covariates: age, sex (nonsex-specific cancers), total household income, employment status, marital status, education, ethnicity, smoking status, body mass index, presence of at least one medical conditions/comorbidity, presence of depression, family history of cancer, sleep duration, and gravidity (breast cancer only). The latency multivariate-adjusted models

removed cancer cases diagnosed <2 years after questionnaire completion. **$p < 0.01$, *$p < 0.05$. HR, hazard ratio; CI, confidence interval.

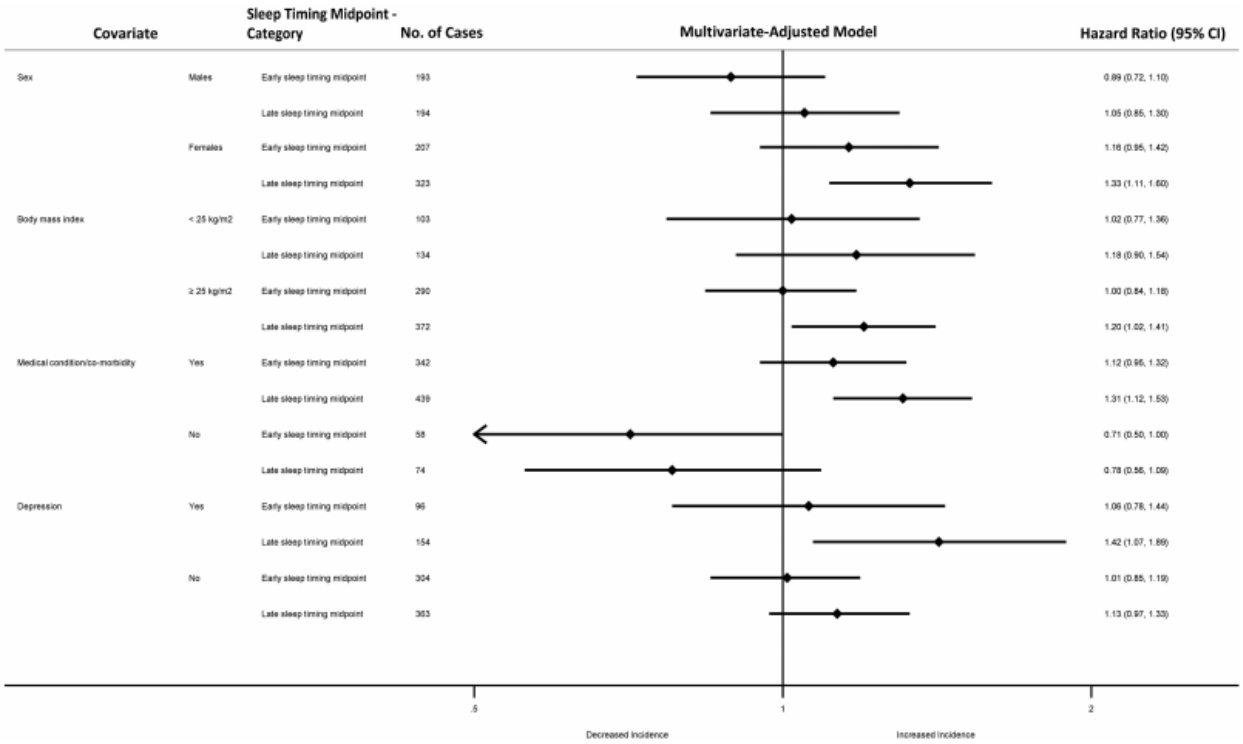


Figure 6. Cox regression hazard ratios of combined cancer incidence and sleep timing midpoint tertiles, stratified by sex, body mass index, presence of at least one medical condition/comorbidity or presence of depression, for 19,822 participants in Alberta's Tomorrow Project.

Note: Intermediate sleep timing midpoint (Ref) = 3 h 47 min–4 h 8 min, early sleep timing midpoint < 3 h 47 min, late sleep timing midpoint > 4 h 8 min. The model was adjusted for age, sex (if not stratified variable), total household income, employment status, marital status, education, ethnicity, smoking status, body mass index (if not stratified variable), presence of at least one medical conditions/comorbidity (if not stratified variable), presence of depression (if not stratified variable), family history of cancer, sleep duration. **$p < 0.01$, *$p < 0.05$. HR, hazard ratio; CI, confidence interval.

We also examined participant characteristics according to sex and case status for 19,822 participants (7,518 males and 12,304 females) included in the sleep timing midpoint analysis (Table 2). Of these, a total of 1,322 participants (585 males and 737 females) developed cancer during the study follow-up period. The mean follow-up times for cancer and noncancer cases were 4.48 ± 4.46 and 8.70 ± 0.22 years, respectively, yielding a total of 166,875 person-years of follow-up. A larger proportion of cancer cases were classified as having a late sleep timing midpoint compared with noncancer cases. Similar to the participants included in the sleep duration analysis, a larger proportion of cancer cases were older, had a higher BMI, were less educated, had a lower total household income, were unemployed, were daily smokers, had at least one medical condition/comorbidity, had a family history of cancer and had >3 full-term pregnancies (females only) compared with noncancer cases.

We investigated the strength of associations between sleep timing midpoint tertiles with combined and site-specific cancer incidence and found that a late sleep timing midpoint was associated with an increased risk of combined cancer incidence in the multivariate-adjusted model (Figure 5). Although no longer statistically significant ($p = 0.07$), a positive association remained between late sleep timing midpoint and combined cancer incidence in the latency multivariate-adjusted model. For breast cancer, a late sleep timing midpoint was associated with an increased risk of cancer in the multivariate- and latency multivariate-adjusted models.

The sleep timing midpoint × medical condition interaction term was associated with combined cancer incidence when added to the multivariate-adjusted model ($p = 0.01$). However, sleep timing midpoint × sex ($p = 0.33$), sleep timing midpoint × BMI ($p = 0.69$) and sleep timing midpoint × depression ($p = 0.16$) interaction terms were not associated with combined cancer incidence in the multivariate-adjusted model. When testing for effect modification, a late sleep timing midpoint was associated with an increased risk of combined cancer incidence in females, but not males, as well as participants with a BMI ≥25 kg/m^2 versus those with a BMI <25 kg/m^2 (Figure 6). Similarly, a late sleep timing midpoint was associated with an increased risk of combined cancer incidence in participants who reported at least one medical condition/comorbidity, but not in participants who reported an absence of medical conditions/comorbidities, as well as participants who reported having depression versus those who reported no depression (Figure 6).

Discussion

This prospective cohort of approximately 45,000 Albertans is the largest to date in Canada to examine the associations between sleep duration and cancer incidence. We observed a U-shaped association between continuous sleep duration and cancer risk. However, the increased HRs for short and long sleep durations, compared with recommended sleep duration, were not statistically significant in the multivariate- and latency multivariate-adjusted models. These results may be partially explained by the small number of self-reported short and long duration sleepers in this cohort (≈25% and 5% of the cohort reported <7 or >9 h of sleep/night, respectively), thus limiting the power to detect associations with cancer risk.

Our findings did show evidence of effect modification by certain covariates, which may undermine some of the abovementioned sleep duration category-cancer incidence associations. The associations for short and long sleep durations were stronger in females compared with males, with a statistically significant association between short sleep duration and combined cancer incidence in females. Specifically, short sleep duration was associated with combined cancer incidence in postmenopausal, but not premenopausal, females. Indeed, recent data from the National Health Interview Survey (Centers for Disease Control and Prevention) reported that women were more likely to report trouble falling asleep and staying asleep, and were more likely to wake up feeling less rested compared with men [67]. A second publication from the same group also reported that postmenopausal women were more likely to sleep <7 h/night, had a higher frequency of difficulty falling and staying asleep, and were less likely to wake up feeling well rested compared with premenopausal women [68]. Some [28, 32], but not all [18, 25, 35], studies have also reported an inverse association between sleep duration and breast cancer incidence in postmenopausal, but not premenopausal, females. It has been hypothesized that the

occurrence of short sleep duration in postmenopausal women may result from the development of possible sleep disturbances and other symptoms (e.g. changes in sex-steroid hormone levels, weight gain, reduced insulin sensitivity) associated with the menopausal transition, which may increase the risk of developing certain types of cancers [69, 70].

We also noted an increased risk of cancer in short sleepers who reported daily alcohol intake, which was not present in participants who reported weekly, monthly, or no alcohol intake. Greater total alcohol intake in short duration sleepers compared with recommended and long duration sleepers was previously reported [62]. Although the causal nature of these associations cannot be determined in this study (i.e. whether daily alcohol intake leads to short sleep duration or being awake for longer leads to more opportunities for alcohol intake), these findings do suggest an interaction between alcohol intake and sleep duration which should be further explored in subsequent studies. Lastly, a statistically significant increase in cancer risk was noted in both short and long duration sleepers who reported at least one medical condition/comorbidity, as well as short duration sleepers who reported living with depression. Both short and long sleep durations have been consistently associated with a number of adverse health outcomes, such as obesity [2–6] and type 2 diabetes [7–9]. Sleep disturbances and short sleep durations are also a common side effect of depression [65, 71, 72]. It may be hypothesized that cancer risk is amplified by short or long sleep durations in individuals with at least one medical condition/comorbidity, including depression. Considering that many of the adverse health outcomes associated with both short and long sleep durations are also risk factors for a number of cancers, these findings could be especially valuable for the design of lifestyle interventions for cancer prevention that target sleep duration in individuals living with comorbidities or depression.

For site-specific cancer risk, long sleep duration was associated with an increased risk of non-Hodgkin lymphoma and hematological cancers in the fully adjusted models. Only one other cohort study assessed the associations between sleep duration and hematological cancers, reporting statistical trends for increased risks of non-Hodgkin lymphoma and myeloma in male short duration sleepers and a suggestive increased risk of non-Hodgkin lymphoma in female long duration sleepers [29]. Considering that long sleep duration can often be confounded by the presence of comorbidities/chronic health conditions and/or poorer sleep quality [15, 26, 49, 50, 73], it is possible that self-reported long sleep duration (or time spent in bed) may be associated with alterations in the immune-inflammation balance [74], thus increasing hematological cancer risk. Subsequent studies are needed to confirm these findings and investigate biomarker changes over time associated with short and long sleep duration for hematological cancer prevention.

Although only available in a subset of the ATP cohort, this study is the first to assess the strength of associations between sleep timing midpoint with combined and site-specific cancer incidence. We observed an increased risk of combined and breast cancer incidence in participants classified as having a late sleep timing midpoint versus an intermediate sleep timing midpoint in the fully adjusted model which included sleep duration as a covariate. Effect modifications were also noted for sex, BMI, and the presence of medical conditions/comorbidities and depression, indicating that participants classified as having a late sleep timing midpoint who were females, had a BMI $\geq$25 kg/m^2, reported having at least one medical condition/comorbidity and reported

living with depression were at an increased risk for cancer. A late sleep timing midpoint has been recently associated with a greater BMI and food consumption in the evening [51], as well as an increased risk of insulin resistance [53] and gestational diabetes [52]. An increased risk of breast [54, 55] or prostate [40, 56, 57] cancers has also been observed in individuals with evening or mixed (i.e. neither morning nor evening) chronotypes compared with a morning chronotype. It has been hypothesized that evening chronotypes may be more susceptible to circadian disruptions and polymorphisms of certain circadian genes (e.g. *Per3* gene) which may lead to tumor development and increase cancer risk [56, 75]. An in-laboratory protocol where 10 females ate and slept according to a "28-hour day," thus inducing circadian misalignment, led to systematic increases in postprandial glucose and insulin levels, coupled with decreases in leptin and sleep efficiency [76]. Variations in cortisol levels were also inverted (e.g. cortisol levels were highest at the beginning of the sleep period when they should be lowest), which may contribute to the observed changes in glycemia responses and leptin levels [76]. Taken together, it is possible that a late sleep timing midpoint, or a misalignment between sleep time and endogenous circadian rhythms, may lead to alterations in metabolic and hormonal profiles. If sustained, these alterations may lead to the development of cardiometabolic conditions (e.g. insulin resistance, obesity), which are also risk factors for a number of cancer sites, including breast [77].

This article has some strengths. Information on a large number of covariates were available in this cohort, and sensitivity analyses were performed by excluding cases diagnosed within 2 years of questionnaire completion. However, there is a risk of residual confounding since information on other covariates shown to be associated with sleep (e.g. current shift work, sleep medication use, habitual physical activity participation) [55–57, 67, 78, 79] were not consistently measured in this cohort. Similarly, menopausal status was not measured with Survey 2008, which contained the only data on sleep timing. Other limitations include the measurement of self-reported sleep duration, bed- and wake-times with questionnaires. Specifically, studies have reported on average moderate-high correlations (0.3–0.75) between self-reported and objectively measured sleep duration, indicating a difference of ≈15–60 min/night in total sleep time between self-reported and objective measurements [80–85]. Lockley *et al.* [80] reported high correlations between subjective and objective measurements of sleep onset (0.77) and offset (0.88), however, lower correlations (≈0.10–0.40) were reported for sleep-wake state transitions (e.g. sleep onset latency, wake after sleep onset) in this study and others [82, 84]. Self-reported errors for sleep parameters may also be more prominent in certain populations (e.g. individuals with self-reported poor sleep quality or a sleep efficiency <85%, high perceived psychological distress, younger age) [83, 85]. Therefore, the use of self-reported sleep measurements may lead to exposure misclassification. However, as previously reported [29], there is no evidence of differences in the occurrence of these reporting errors by cancer status, meaning that any exposure misclassification may bias our results toward the null. The small number of cases for certain cancer sites within the short and long sleep duration categories may have reduced the statistical power to detect an association. There is a risk of health literacy bias since only those participants who were able to comprehend, complete, and return the study questionnaires were included in this study.

These findings suggest that sleep duration and sleep timing may play a role in cancer etiology. Furthermore, effect modification results suggest that other biological and behavioral components

may directly impact the association between sleep duration and sleep timing with cancer incidence, and should be considered in future reports within this research area. Additional studies including objective assessments of sleep are needed to corroborate these findings and inform future health promotion efforts on sleep as a potentially modifiable risk factor for cancer.

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Conflict of interest statement. None declared.

Work Performed: Department of Cancer Epidemiology and Prevention Research, CancerControl Alberta, Alberta Health Services, Calgary, Alberta, Canada

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